REMARKS

Claims 1-27 are rejected under 35 U.S.C. § 112, first paragraph. The examiner appears to be asserting that the process is only enabled for steps (a) and (b) which involve heating and/or stirring, and not "without any additional supply of energy".

Claims 1-27 are also rejected under 35 U.S.C. § 112, second paragraph, the examiner asserting that carrying out steps (a) and (b) without any additional supply of energy violates basic thermodynamic laws.

Applicants teach:

> Step (α) is usually carried out at room temperature, where necessary with heating and under normal pressure conditions. Mixing is carried out using standard [or conventional] stirring apparatus, for example propeller, angled paddle or magnetic agitators, and without using any special mechanical stirring aids.

Applicants further teach:

> Step (β) is carried out by adding the liquid obtained in step (α), the nanodispersion prephase, to the water phase of the pharmaceutical end formulations. The particular choice of components (a), (b) and (c) results directly in ultrafine, monodisperse nanodispersions. In this case it is possible to forego homogenisation via nozzle, rotor-stator or ultrasound homogenisers, which is usually carried out to convert coarsely disperse or at least heterodisperse systems to fine monodisperse systems. Step (β) is thus characterised by the absence of high shear or cavitation forces. [Emphasis added]

Responsive to the examiner's comments, applicants concede that the optional heating and/or conventional low shear stirring in step (α), provide some small amount of energy. Additionally, step (β) is carried out by adding the liquid obtained in step (α), the nanodispersion prephase, to a preheated water phase (see examples 8ff) with conventional low shear stirring. Thus some thermal and some minimal mechanical energy are also supplied in step (β). No violation of basic thermodynamic laws is taught. However applicants do clearly teach that the high shear or cavitation forces employed in homogenisation via nozzle, rotor-stator or ultrasound homogenisers are not needed to obtain the inventive aqueous nanodispersions of pharmaceutical formulations.

Accordingly applicants have amended their claims in order to more particularly point out and distinctly claim their invention. Thus, the limits of originally filed claims 1, 3, 4, 7, 11-14 and 26 have been combined into new independent method claim 28. Claim 28 is supported by the claims mentioned and the corresponding disclosure as well as the teachings cited supra. It is additionally noted that in all of the working examples the pharmaceutical active agent is lipophilic and is always present as component (c), Since claims 1, 3, 4, 7, 11-14 and 26 fail to further limit claim 28, they have been presently cancelled.

Claim 29 replaces claim 27 and parallels claim 28. No new matter has been added.

Applicants aver that the claims as amended are fully responsive to all grounds of rejection under 35 U.S.C. § 112, first and second paragraphs. Thus terms such as "using" and "so-called nanodispersion prephase" no longer appear. Re claim 5, "O/W" means "oil-in-water", and one skilled in the art would know this. However claim 5 now recites as component (b) the specific substances formerly recited in claim 8. Since claim 8 fails to further limit amended claim 5, it has been presently cancelled. Additionally, claim 17 now recites "oil-in-water emulsion, water-in-oil emulsion" in place of the abbreviations. The word "end" has been deleted from "pharmaceutical end formulation", and the water phase no longer refers to " of the pharmaceutical end formulations" since said water phase does not contain the lipophilic pharmaceutically active agent. Rather it is always present in component (c). No claims are directed to a nanodispersion prephase, and claims 22 and 23 have been presently cancelled.

It is respectfully submitted that all the claims submitted for reconsideration are in good formal order. Reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §112, first and second paragraphs is therefore solicited.

Claims 1-3, 5-13, 15-17, 20-21 and 25-27 are rejected under 35 U.S.C. § 102(b) as being anticipated by "5,171,566". This appears to be U.S. Patent 5,171,566 (Mizushima et al.). It is respectfully noted that U.S. Patent 5,171,566 was not of record and no copy was provided. Applicants respectfully traverse this rejection with regard to the instant claims.

Mizushima et al. teaches to prepare water-in-oil emulsions with a homogenizer, for example a pressure jet (nozzle) or ultrasonic homogenizer. See col. 3, lines 23-26 and the examples which

employ a Manton-Gaulin high shear, high pressure jet homogenizer. In contrast thereto, the inventive nanodispersions are prepared by a process "wherein step (β) is carried out in the absence of high shear or cavitation forces". Thus the claimed process is neither taught nor suggested by Mizushima et al.

Reconsideration and withdrawal of the rejection of claims 1-3, 5-13, 15-17, 20-21 and 25-27, now claims 2-3, 5-6, 9-10, 12, 15-21, 24 and 28-29, under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent 5,171,566 (Mizushima et al.) is respectfully solicited in light of the remarks *supra*.

Claims 25-27 are rejected under 35 U.S.C. § 102 as being anticipated by U.S. Patent 5,338,761 (Nakajima et al.). Applicants note that claims 25 and 26 have been presently cancelled and claim 29 replaces claim 27. Applicants respectfully traverse this rejection with regard to claim 29.

Nakajima et al. teaches to effect emulsification with an emulsifying machine capable of providing a strong shearing force, such as a high pressure homogenizer or sonication emulsifying machine. See col. 4, lines 17-20. In the examples the formulation is repeatedly cycled through a high pressure jet homogenizer at a pressure of 900 atmospheres. See col. 5, lines 32-35. Thus the claimed process is clearly neither taught nor suggested by (Nakajima et al.).

Reconsideration and withdrawal of the rejection of claims 25-27, now claim 29, under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent 5,338,761 (Nakajima et al.) is respectfully solicited in light of the remarks *supra*.

Claims 1-27 are rejected under 35 U.S.C. § 102(b) as being anticipated, or in the alternative as obvious over U.S. Patent 5,633,226 (Owen et al.). Applicants respectfully traverse this rejection with regard to the instant claims.

Owen et al. discloses water-in-oil microemulsions comprising
(a) an aqueous phase,
(b) a pharmaceutically acceptable oil or mixtures thereof,
(c) an oil-dispersible surfactant and
(d) a water-soluble biologically active material or combination of materials.

It is the clear teaching of Owen that the biologically active material is always water soluble. Owen teaches at col. 5, lines 57ff:

> The formulation of a microemulsion having a high aqueous phase content is preferred in those situations where the biologically-active material has a relatively low solubility in water or where a relative high quantity of the biologically-active material is desired in the microemulsion.

The water-soluble active material which is incorporated in the internal aqueous phase of the w/o emulsion is taught more specifically in col. 7, lines 60ff: water-soluble proteins, peptides and other pharmaceutically-active compounds. Furthermore, water-soluble drugs can be employed (col. 8, line 14).

The requirement of water solubility of the biologically active material is clearly disclosed in col. 9, lines 53 to 59:

> The biologically active material is said to be "water-soluble" material. Those skilled in the art will readily understand by the list of representative active materials that they are soluble to an effective extent in an aqueous phase and have negligible solubility in an organic phase. The solubility of the active materials in the aqueous phase at about 20°C is at least about 1 part per 100.000 parts and preferably at least 1 part per 10.000 parts.

In contrast thereto, in the presently claimed methods and compositions the pharmaceutically active agent is lipophilic and always present as component (c). This can be seen from the working examples wherein the pharmaceutical active ingredients are always lipophilic substances. This is clearly unsuggested by Owen.

Additionally, Owen is silent about compositions comprising as an essential component a C_2-C_8alcohol. Hence no contemplation of the teachings of Owen would have motivated a person of ordinary skill in the art to use lipophilic pharmaceutical ingredients for microemulsions or nanodispersions.

Reconsideration and withdrawal of the rejection of claims 1-27, now claims 2, 5-6, 9-10, 15-21, 24 and 28-29 under 35 U.S.C. § 102(b) as being anticipated, or in the alternative as obvious over U.S. Patent 5,633,226 (Owen et al.) is respectfully solicited in light of the remarks *supra*.

Since there are no other grounds of objection or rejection, passage of this application to issue with claims 2, 5-6, 9-10, 15-21, 24 and 28-29 is earnestly solicited.

Applicants submit that the present application is in condition for allowance. In the event that minor amendments will further prosecution, Applicants request that the examiner contact the undersigned representative.

Respectfully submitted,

Kevin T. Mansfield

Ciba Specialty Chemicals Corporation
540 White Plains Road
Tarrytown, New York 10591
(914) 785-7127

Kevin T. Mansfield
Agent for Applicants
Reg. No. 31,635

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Enclosure: Claim of Priority, Petition for Extension of Time, Information Disclosure Statement and PTO-1449 form.

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